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REPORTS ON HYPERTENSION

Improved Left Ventricular Filling Accompanies Reduced Left Ventricular Mass During Therapy of Essential Hypertension

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Abnormal left ventricular diastolic performance, an early manifestation of hypertension in the heart, may precede the development of left ventricular hypertrophy. To assess effects of antihypertensive therapy on the heart, left ventricular mass (determined by echocardiography) and rapid left ventricular filling rate (determined by radionuclide ventriculography) were compared before and after 6 months of treatment of 16 patients. Nitrendipine (a dihydropyridine calcium channel blocker) was given alone or in combination with either propranolol or hydrochlorothiazide, or both, and significantly reduced blood pressure (156/103 ± 12/7 to 137/89 ± 10/6 mm Hg).

In 6 of the 16 patients, left ventricular mass decreased by more than 10% (270 ± 95 to 193 ± 47 g, $p < 0.01$); in the same patients, left ventricular filling rate increased (2.03 ± 0.35 to 2.30 ± 0.45 end-diastolic counts/s [EDC/s], $p < 0.01$). In the one patient whose left ventricular mass increased (137 to 195 g), left ventricular filling rate decreased from 2.01 to 1.78 EDC/s. In the remaining nine patients who had no change in left ventricular mass, there was no significant change in left ventricular filling.

The changes in ventricular mass and filling could not be related to the extent of change in blood pressure or heart rate. These data suggest that regression of left ventricular mass during antihypertensive therapy with nitrendipine is accompanied by improved diastolic function.

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Abnormalities of both systolic (1–3) and diastolic (4,5) performance that appear during chronic left ventricular pressure overload are generally proportional to the degree of left ventricular hypertrophy. However, impaired left ventricular filling can occur in the absence of echocardiographically defined hypertrophy and may represent an early marker for the pathologic effects of hypertension on the myocardium (6–8). The present study was undertaken to determine whether antihypertensive therapy reduces ventricular mass, and whether these changes correlate with improved left ventricular filling in hypertensive patients.

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Methods

Study patients. Twenty-two patients with mild to moderate essential hypertension (supine diastolic blood pressure between 90 and 115 mm Hg in the untreated state) were recruited from the Hypertension and Cardiology Clinics of the John Dempsey Hospital. Sixteen patients (mean age 46 ± 11 years; 14 men and 2 women) who had echocardiograms of acceptable quality for serial ventricular mass calculations formed the study group. None of these patients had a history of angina pectoris, myocardial infarction or valvular heart disease, and none had evidence of coronary artery disease by electrocardiography, radionuclide exercise ventriculography or thallium scintigraphy. None of these patients met electrocardiographic criteria for left ventricular hypertrophy. Other patient characteristics are listed in Table 1. The study was approved by the University of Connecticut Institutional Review Board and all subjects gave informed consent.

Antihypertensive therapy protocol (Fig. 1). Antihypertensive medications were withdrawn for 2 weeks, after which the patients received placebo for 4 weeks. Baseline measurements were taken during the fourth week of placebo therapy. The study protocol required reduction of supine

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Table 1. Patient Characteristics and Principal Findings

	Placebo	Treatment
Heart rate (beats/min)	64 ± 7	68 ± 8, $p < 0.02$*
Systolic blood pressure (mm Hg)	156 ± 12	137 ± 10, $p < 0.01$
Diastolic blood pressure (mm Hg)	103 ± 7	89 ± 6, $p < 0.01$
LV mass (g)	246 ± 94	222 ± 64, p = NS
LV filling rate (EDC/s)	1.95 ± .34	2.11 ± .54, $p < 0.05$
LV ejection fraction (%)	60 ± 4	59 ± 4, p = NS

*All probability values compare treatment with placebo. EDC = end-diastolic counts; LV = left ventricular.

diastolic blood pressure to less than 90 mm Hg if the baseline blood pressure was greater than 100 mm Hg, or a reduction of 10 mm Hg if the baseline diastolic blood pressure was between 90 and 100 mm Hg. All patients were started on treatment with nitrendipine at a dose of 5 mg twice daily with weekly titration to a maximal daily dose of up to 80 mg to achieve the blood pressure goal. If nitrendipine monotherapy failed to achieve the goal blood pressure, a second drug was added: propranolol (up to 160 mg/day) or hydrochlorothiazide (up to 50 mg/day), or both. The maximal time of nitrendipine monotherapy before the addition of a second drug was 3 weeks. For patients taking hydrochlorothiazide, oral potassium chloride supplements were administered when the serum potassium level fell below 3.5 mEq/liter.

Blood pressure and heart rate determinations. Heart rate (electrocardiogram) and blood pressure (mercury column sphygomomanometer) were measured when the patients were supine for at least 5 minutes. The values reported as the treatment response represent the average data from two visits 2 to 4 weeks apart after 6 months of drug therapy.

Left ventricular mass. At the end of the placebo period, and again after 6 months of antihypertensive drug therapy, an M-mode echocardiogram was obtained. Calculations of left ventricular mass were made from left ventricular dimensions obtained using the Penn measurement conventions according to the method of Devereux and Reichek (9). The relevant dimensions of three cardiac cycles were averaged to form the basis of the mass calculation. Baseline and treatment records were obtained during held expiration in the same body and transducer positions. Patients took their study medications on the day of the treatment echocardiogram. All echocardiograms were coded and read blindly in random sequence by a single observer (V.S.).

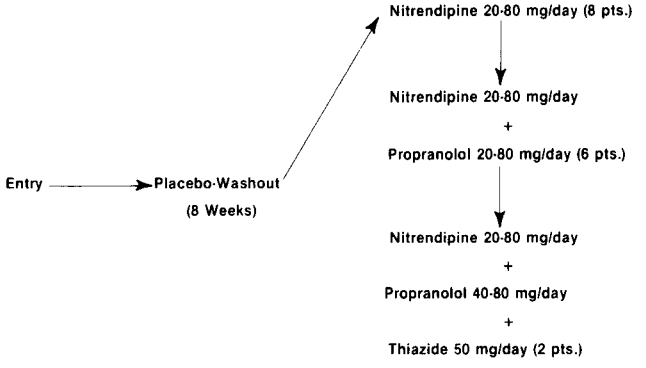
To determine intraobserver variation, 10 sample echocardiograms were again read by the observer after an interval of 3 months. For the purposes of this study, variability was determined in the following manner: The difference in left ventricular mass between the first and second reading of a given echocardiogram, divided by the mass obtained in the first reading was the percent variation of the second reading. The percent variation of the 10 sample echocardiograms was then averaged; 2 standard deviations (2Z) were added to the mean (X) of this calculation and multiplied by 100%. The result was considered the percent variability ($X + 2Z \times 100\%$) for reading any two echocardiograms based on the assumption that they were otherwise identical.

A "responder" was defined as a patient whose left ventricular mass on the baseline echocardiogram exceeded the value from the treatment echocardiogram by more than the percent variability associated with the control echocardiograms. "Nonresponders" failed to show this extent of mass reduction.

Left ventricular filling. Rapid left ventricular filling was studied at the end of the placebo period and within 3 days of the "treatment" echocardiogram. To avoid immediate hemodynamic effects of the drugs, patients were withdrawn from treatment for 24 to 48 hours before the radionuclide studies. After the patient's red blood cells were labeled with technetium-99m, average rapid left ventricular filling rates were calculated from nuclear probe-derived high resolution time-activity curves with gamma camera validation of the left ventricular region of interest as described elsewhere (4). The results of three separate determinations of the region of interest and the background constituted a session and were averaged for the baseline and treatment values, respectively. For the purposes of this study, the percent variability that could be attributed to any session was calculated as follows: The mean and standard deviation for the three determinations of filling rate in a session were calculated. The value of 2 standard deviations (2Z) was divided by the mean value for filling rate for the session (X) and multiplied by 100%, yielding a percent of the mean filling rate (%LVFR): $\%LVFR = 2Z/X \times 100\%$. The percent of the mean filling rate was averaged for 10 control sessions.

A "responder" was defined as a patient in whom the difference between the placebo and treatment rapid left ven-

Figure 1. Study design (16 patients). The treatment objective was to reduce diastolic blood pressure by 10 mm Hg if the baseline diastolic blood pressure was 90 to 100 mm Hg, or to less than 90 mm Hg if the baseline diastolic blood pressure was greater than 100 mm Hg.



tricular filling rate exceeded the mean percent of the mean filling rate for the control sessions and was not associated with a significant change in heart rate or ejection fraction. The method to determine variability of left ventricular filling rate differed from that used to assess intraobserver variability for echocardiograms because in the former, the variability results from selection of the region of interest and background, whereas in the latter, variability results from observer choice of recorded echoes.

Ejection fraction was calculated by dividing the stroke counts by end-diastolic counts with subtraction of the background activity. In our laboratory intraobserver variability has been established at less than 3 absolute percent.

Statistical methods. The effect of antihypertensive therapy on left ventricular mass and filling rate for the entire group of 16 patients was evaluated by means of a paired *t* test. A two-tailed *t* test was used to characterize any differences in the blood pressure, heart rate and ejection fraction responses to treatment of responders and nonresponders. Statistical evaluations of the effects of individual treatment regimens on responders and nonresponders with respect to left ventricular mass and left ventricular filling were not done in view of the small number of subjects in each group.

Results

Variability of left ventricular mass and filling studies. The mean (X) of the difference in ventricular mass between the first and second readings of the same echocardiogram expressed as a percent of the baseline value was, for 10 echocardiograms, 0.04 ± 0.03%. Thus the variability due to the observer was considered to be a maximum of 10%. For the radionuclide studies of rapid ventricular filling, the value of 2 standard deviations of a session divided by the mean was 0.042 when 10 sessions were averaged. Thus, the maximal within-session variability resulting from selection of region of interest and background was considered to be 4%.

Blood pressure and heart rate. The effects of antihypertensive therapy on heart rate and blood pressure are shown in Table 1. All patients achieved the goal of therapy. There were no differences between responders and nonresponders (in regard to either left ventricular mass or filling) with respect to reduction of blood pressure after therapy (19 ± 8 versus 20 ± 7 mm Hg systolic, and 17 ± 4 versus 19 ± 6 mm Hg diastolic, respectively, both p = NS (Fig. 2). Even though the subjects had not taken antihypertensive drugs for 24 to 48 hours at the time of the treatment radionuclide filling studies, systolic blood pressures remained slightly lower than the baseline values (148 ± 16 versus 158 ± 13 mm Hg, $p < 0.05$) but were similar in patients whose filling rate increased and in those in whom it did not. A slight increase in heart rate at rest was noted during antihypertensive therapy when all patients were considered as a single group (64 ± 7 versus 68 ± 8, $p < 0.02$), but no differences in heart rate after drug therapy were seen in the responders and the nonresponders (with respect to ventricular mass and filling) (2 ± 5 versus 4 ± 6 beats/min, p = NS) (Fig. 2). Further, the differences in heart rate abated after ½ hour at rest, and thus were not a factor during radionuclide studies (Table 1).

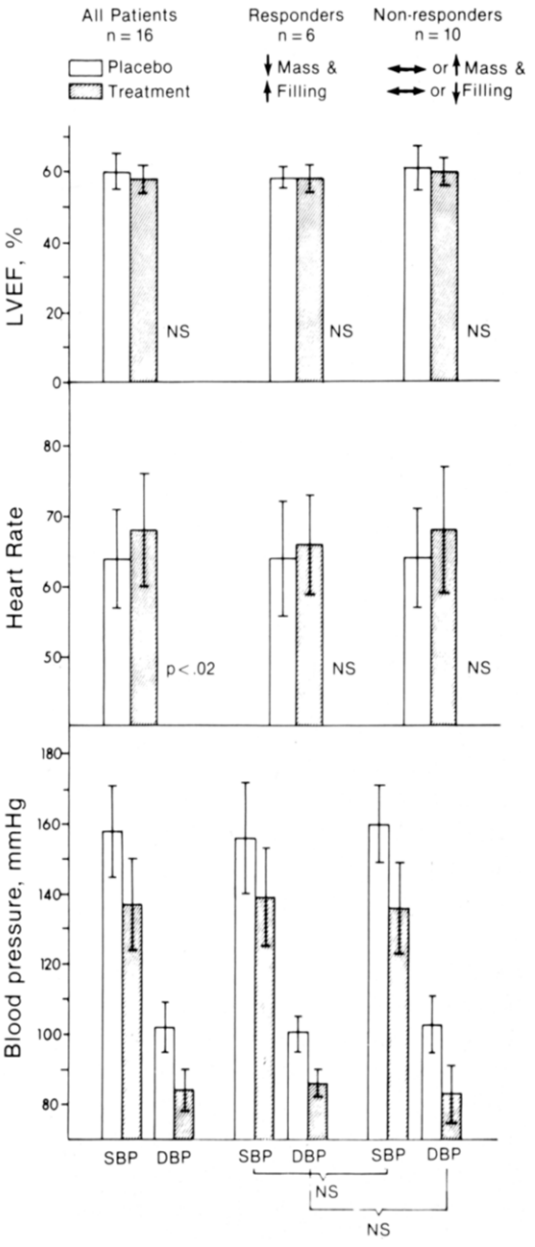


Figure 2. Left ventricular ejection fraction (LVEF), heart rate and systolic (SBP) and diastolic (DBP) blood pressure during placebo and active therapy. Responders are classified by left ventricular mass change and are compared with nonresponders.

Left ventricular wall thickness, chamber dimensions and mass. Patterns of change were variable; the study group was not large enough to justify grouping patients as re-

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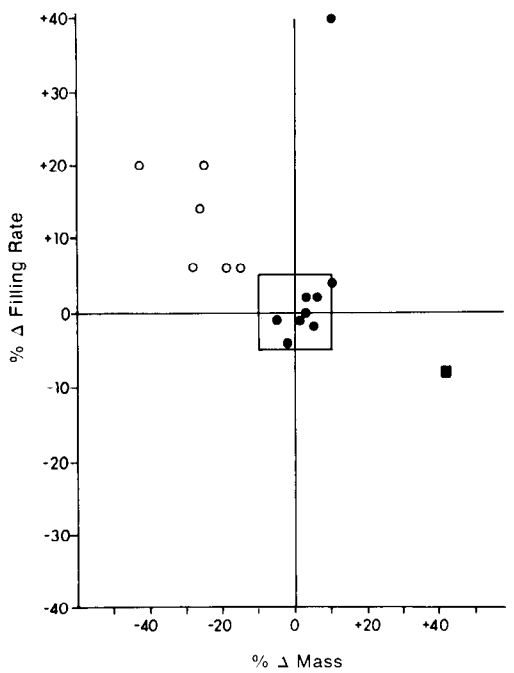
sponders with respect to changes in geometry of the ventricle. Because the variability of mass attributable to the observer was 10% in control echocardiograms, "mass responders" were defined as those patients whose ventricular mass declined by more than 10% (mean plus 2 standard deviations). Left ventricular mass for the study group as a whole did not change significantly after treatment (246 ± 94 versus 222 ± 64 g) (Table 1). However, in the six responders the average left ventricular mass change was −26 ± 9%; whereas 9 of the 10 nonresponders had a small increase in left ventricular mass of 5 ± 4%, one nonresponder had an increase of 41% (Fig. 3).

Left ventricular filling rate and ejection fraction. For the entire study group, the average rapid left ventricular filling rate improved from 1.95 ± 0.34 to 2.11 ± 0.54 end-diastolic counts/s (EDC/s), $p < 0.05$ (Table 1). As the variability of average rapid left ventricular filling rate determinations noted from control sessions was 4%, "filling rate responders" were defined as patients whose filling rate increased by more than 4% of the baseline value after antihypertensive therapy. Filling rate improved in seven patients (mean 0.26 ± 0.20 EDC/s, $p < 0.02$), did not change in eight (0.12 ± 0.31 EDC/s, p = NS) and decreased in one patient (0.14 EDC/s) (Fig. 3). With the exception of one patient, the changes in filling rate were not associated with changes in ejection fraction (Fig. 2). Whereas heart rate at the 6 month treatment visit was slightly higher than at baseline because some patients were withdrawn from treatment, heart rate measured during gated acquisition was not different from baseline (68 ± 7 versus 67 ± 8 beats/min, p = NS).

Figure 3. Changes in left ventricular mass and average rapid left ventricular filling rate during antihypertensive therapy. **Open circles** represent the responders, **closed circles** and **closed square** represent the nonresponders (see text). The **middle box** defines the limits of intraobserver variability for the echocardiographic and radionuclide studies.



Relation between changes in left ventricular mass and filling. There was an inverse relation between the changes in left ventricular mass and those in left ventricular filling rate (Fig. 3). The one patient whose filling rate increased 40% without a change in mass after treatment also had a 48% increase in heart rate and an absolute 12% increase in ejection fraction in the posttreatment study. This outlier may therefore have experienced excessive sympathetic tone during the posttreatment study.

Discussion

Principal findings. This study indicates that patients whose left ventricular mass decreases during antihypertensive therapy also experience improved left ventricular filling. Conversely, those patients who do not manifest a reduction in left ventricular mass show no improvement in diastolic function.

Significance of the findings. Changes in left ventricular mass during antihypertensive therapy have been frequently studied in recent years (10–12), but related changes in left ventricular function are less well described. Because impaired diastolic performance is characteristic of the ventricle that becomes hypertrophic in response to a chronic pressure overload (6–8), the finding of improved diastolic function that parallels regression of left ventricular mass is important, implying reversal of pathophysiologic processes in the hypertensive left ventricle.

In this and previous studies (13,14) responses of left ventricular mass to antihypertensive therapy were heterogeneous. In light of these varied responses, it is always possible that the measured changes in ventricular mass were due to variability of measurements rather than to real changes in left ventricular mass itself. However, the finding of parallel improvement in diastolic ventricular function by an entirely independent method suggests that the changes (or lack thereof) in echocardiographically measured mass corresponded to the actual state of the ventricular muscle itself. Thus, measurements of left ventricular filling by radionuclide techniques may provide a way to validate changes in ventricular mass measured echocardiographically.

Previous studies. Inouye et al. (15) were unable to consistently demonstrate improvement in diastolic function after 4 months of antihypertensive drug treatment in 10 patients using diuretic, beta-adrenergic blocking and calcium channel blocking agents, but 7 of 10 patients in their study had an improvement in the first third filling fraction during diltiazem treatment. They emphasized the failure of a con-

sistent response, but an alternative interpretation of their results would be that response to treatment was variable.

Heterogeneity of responses. A number of explanations could account for the differences in the structural and functional responses of the left ventricle to reduction of blood pressure observed in our study. Left ventricular mass regression does not always occur in response to reduction in blood pressure alone (16), and Kobrin et al. (17) reported a dissociation of changes in left ventricular mass from blood pressure responses to nitrendipine in rats. It is also possible that the casual (office) blood pressures reported in this study do not adequately represent the average daily blood pressure "experienced" by the left ventricle (18,19). Devereux et al. (20) showed that the correlation between blood pressure and left ventricular mass is improved when 24 hour ambulatory blood pressures are recorded. A comparison of response rates based on drug regimen in our study would not be meaningful because the number of patients in each treatment group was small. Further, the duration of therapy was only 6 months, which may be too short a study interval to demonstrate regression of mass in some individuals (21). Finally, failure of a particular patient to demonstrate regression of left ventricular mass after a reduction in blood pressure could be due to the presence of a pathologic state wherein normalization of structure is no longer possible.

Possible mechanisms for improved diastolic function. In the chronically pressure-overloaded ventricle a mismatch between energy supply and demand could result in impaired relaxation through a decline in high energy phosphate levels. Reduced afterload could, by restoring oxygen supply/demand balance and augmenting adenosine triphosphate supply, enhance relaxation (22). Additionally, regression of left ventricular mass may have restored a more favorable ratio of effective capillary surface to myofibrillar mass. Finally, because all of the patients who participated in the study were taking nitrendipine, it is possible that this calcium channel blocker, by reducing the amount of calcium released within the cytosol from a relatively energy-deprived sarcoplasmic reticulum, could have enhanced muscle relaxation by a mechanism that was independent of its effect to reduce afterload. A more precise understanding of the mechanisms responsible for improved ventricular relaxation during therapy with nitrendipine will require comparative studies with drugs having equal antihypertensive potency but with a mechanism of action not involving blockade of calcium entry into the cell.

Clinical significance of the findings. Left ventricular diastolic function improves in association with the regression of left ventricular mass (Fig. 3) after antihypertensive therapy, and this phenomenon may occur independently of the extent of reduction in blood pressure. Studies of diastolic ventricular function may provide an important and sensitive means to identify desirable target organ responses to antihypertensive therapy, as well as to detect subtle changes of cardiac function in hypertensive individuals. Larger therapeutic trials will be required to delineate the ultimate usefulness of this technique and to identify the variables predicting favorable responses of diastolic function to antihypertensive therapy.

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